Addiction Medicine
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The New Disease Model of Alcoholism

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The new biopsychosocial disease model of alcoholism is examined from the perspective of recent biologic research. Studies of animal and human genetic predispositions suggest the presence of genetic influences over drinking behavior as well as biologic risk factors related to deficiencies in various neurochemicals. Ethanol affects the fluidity of cell membrane lipids, eventually causing membrane dysfunction. It also adversely affects the activity of two enzymes, monoamine oxidase and adenylate cyclase, that have important functions in the information processing system of the brain. Research on condensation products formed in the brain after alcohol consumption has provided clues to the development of alcoholism, but many questions remain unanswered. Alcoholism is clearly a multidimensional phenomenon in which biologic, psychological, and sociocultural factors interact to produce illness.

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In recent years, considerable progress has been made in conceptualizing alcoholism as a disease. This modern disease model is multidimensional and incorporates biologic, psychological, and sociocultural factors. Alcoholism is increasingly being viewed as a biopsychosocial illness in which genetics, neurochemistry, pharmacology, behavior, and social environment are involved.[1-4] In this article I discuss recent work concerning the biologic dimension of the biopsychosocial model of alcoholism.

Animal Behavioral Genetic Studies

Selective breeding and genetic selection techniques have been used successfully to develop strains of mice and rats that differ in alcohol-related behaviors.[5,6] A preference for alcohol over water and a differential sensitivity to the drug have been shown to be genetically influenced. The C57BL/6 mouse strain shows a tendency to prefer alcohol to water, whereas the DBA/2 strain does not. Another strain, the "short-sleep" mouse, shows considerable resistance to alcohol's effect on the righting reflex while the "long-sleep" mouse appears highly vulnerable to this drug effect.

In studies of short-sleep and long-sleep mice, a 30-fold increase in a dose of alcohol is required to produce the same level of impairment in Purkinje's neurons of short-sleep mice evident in long-sleep mice at much lower doses.

Li and colleagues have developed two strains of rats, the "alcohol-preferring" and "alcohol-nonpreferring" strains.[7] Li points out that for animal models of drinking behavior to have relevance to alcoholism in humans, the following criteria must be met: the animals must seek out alcohol, ingest it orally, engage in efforts to get the drug, develop a tolerance to alcohol, and become physically dependent on it. Li's alcohol-preferring rats show all of these criteria.

Hence, recent studies of animal behavioral genetics indicate that considerable genetic influences on animal drinking behavior exist and enter into alcohol preference and a differential sensitivity to alcohol. Studies of drugs other than alcohol have shown similar results. In fact, for all drugs investigated, significant genetic differences in drug self-administration have been found.[8] Among the opioids, genetic differences in the self-administration of morphine, codeine, and etonitazene have been shown in animals. Genetic differences in cocaine self-administration, locomotor activation, lethality, and the incidence of cocaine-induced seizures have also been found.

Recent Human Genetic Studies

Human genetic studies are consistent with animal studies in showing genetic influence. Schuckit has found that sons of alcoholic parents appear less sensitive to some psychomotor effects of ethanol than are sons of nonalcoholic parents.[9] Sons of alcoholic parents showed significantly less body sway and differences in hormonal reactions and gave fewer subjective reports of intoxication compared with sons of nonalcoholic parents when both groups received identical amounts of alcohol.

Cloninger and colleagues used adoption-study techniques to investigate genetic influences in etiology.[10] When Swedish adopted children of alcoholic and nonalcoholic parents were studied, substantial genetic influences were shown for two different types of alcoholism. Type I alcoholics showed a later onset of the disease, little or no criminality, and a threefold increased risk for alcoholism and appeared to require an interaction between genetics and environment for the development of the disease.

In type II alcoholics, the disease began early, was associated with considerable criminal behavior, and there was a ninefold increase in the risk for alcoholism. In contrast to type I alcoholics, type II alcoholics did not require environmental factors for the disease to develop. For this particular

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set of empiric observations, genetic factors alone were sufficient to produce the illness in type II alcoholics.

Cloninger's data also pointed to a genetic factor for alcoholism in women. Earlier adoption studies by Goodwin and colleagues in Denmark had shown genetic influence in alcoholism in men but not in women.[11] Goodwin's samples, however, had included few mothers and daughters. Cloninger's samples included a sufficient number of women for the question of genetic influence on alcoholism in women to be considered. When the biologic mothers in Cloninger's study were alcoholics, daughters showed a threefold increase in the incidence of alcoholism. Daughters of biologic alcoholic fathers also showed an increased risk for alcoholism, but not as substantial an increase as seen in biologic mothers and daughters.

The Search for Biologic Risk Factors

While genetic influence has been demonstrated, the precise nature of genetic risk factors remains unknown. There are promising leads, however. In rats, alcohol preference has been consistently related to deficiencies in serotonergic neurotransmission. Li and associates have shown consistent deficiencies in serotonin in particular brain locations (cerebral cortex, thalamus, hypothalamus, hippocampus, and corpus striatum).

These findings of genetic differences in serotonin are consistent with experimental studies involving increases and decreases in serotonin in animals and humans. When the serotonin level is reduced, ethanol consumption has been shown to increase.[12] Conversely, when the serotonin level is raised, ethanol consumption was found to decrease.[13]

Studies of other neurotransmitters and neuromodulators suggest involvement of other brain chemicals in addition to serotonin. Blum and co-workers have reported an association between enkephalin levels and ethanol preference in mice.[14] Moreover, this relationship between levels of a brain opioid peptide and ethanol consumption appears to be genetically influenced.

In Sweden, Borg and colleagues reported a possible role for noradrenergic neurotransmission in the relapse to active alcoholism among those recovering from alcoholism.[15] Paradoxically, alcoholic persons with *lower* noradrenergic activity three to six months into recovery showed higher rates of relapse.

The search for biologic risk factors in alcoholism is complicated by the considerable heterogeneity apparent in both clinical and nonclinical samples of alcoholics and problem drinkers. It is entirely possible that different biologic types exist and that different groups of risk factors will prove necessary to account for this apparent heterogeneity. Hence, while one type may show problems in serotonergic neurotransmission, another type may show disturbances in dopaminergic neurotransmission. Elsewhere I argue that persons with alcoholism may differ greatly in activation or arousal levels, with one type showing excessive arousal and another type showing levels of arousal so low that they border on outright anhedonia.[16(p9)]

As a consequence, some persons with alcoholism may relapse in response to excessive stimulation, stress, and high arousal-related discomfort whereas others may drink in response to boredom, restlessness, and an inability to experience pleasure. Different types of alcoholism may produce different underlying neurochemical deficits; these, in turn, may be related to different genetic risk factors.

Cloninger's data pointed to the possibility that certain inherited personality characteristics distinguishing type I from type II alcoholics may constitute genetic risk factors. Type I alcoholics are thought by Cloninger to be high in the traits of harm avoidance and reward dependence and low in the trait of novelty seeking. Type II alcoholics are low in the traits of avoiding harm and reward dependence but score high on the measures of the trait of novelty seeking. Cloninger thinks that these genetically influenced differences in personality traits and associated differences in neurochemistry constitute the important genetic risk factors for alcoholism.

Genetics of Alcoholism: A Summary

I have summarized recent research on genetics and alcoholism as follows:

- Research in genetics has contributed strong evidence in favor of a disease model of alcoholism;
- Various predispositions, risk factors, or vulnerabilities to the disease are inherited, although alcoholism per se does not appear to be;
- These genetic predispositions or risk factors come into play as people consume more and more alcohol;
- Environment must also play a role in causation because not everyone in whom alcoholism develops has a positive family history of the disease;
- In many cases of alcoholism, the roles played by culture and society acting alone or in concert with genetics must be explored;
- Differences between and among various alcoholics may be related to underlying differences in neurochemistry.

Cell Membrane Research

When large amounts of alcohol are forced into a cell membrane, the fatty bilayers that make up the membrane become even more fluid than they normally are. These disturbances of the cell wall fluidity by alcohol are thought by some to be the biologic basis of intoxication. In adapting to this increased fluidity, the cell stiffens. This stiffening of the cell wall is thought to be the biologic basis of tolerance to alcohol ("tolerance" refers to the need for larger doses of a drug to get the same effect). Finally, as a person drinks larger and larger quantities of alcohol, the cell wall becomes rigid. At this point the cell membrane becomes hyperexcitable and the person is in danger of having a seizure. It has been hypothesized that rigid cell membranes in the brain are the biologic basis of physical dependence.[17]

Some researchers argue that alcohol acts directly on the large protein molecules embedded in the lipid bilayers of cell membranes and that it is these direct actions on proteins that are important, rather than the changes taking place in the fatty bilayers of the membranes.[18]

Whether alcohol's most important effects are on the lipids making up the cell wall or on the proteins embedded in these lipids is a highly technical question that can only be resolved by further research. The implication here seems clear, however. Alcohol is a drug that can and does affect major brain structures and processes. These changes in the brain that occur with heavy drinking are what is meant, in part, when it is said that alcoholism is a disease.

Monoamine Oxidase and Adenylate Cyclase

Recent research has also looked at certain enzymes involved in the brain's information-processing system. Monoamine oxidase and adenylate cyclase are two important enzymes. Monoamine oxidase is important because it is crucial to the metabolism and turnover of the neurotransmitters dopamine, noradrenaline, and serotonin. A deficiency in monoamine oxidase or a decrease in its activity results in problems in brain function.

Adenylate cyclase plays a vital role in changing neurotransmitters after they have left one neuron, passed through the synapse, and linked up to the receptor on the surface of a second neuron. Adenylate cyclase does this by triggering the synthesis of the "second messenger," cyclic adenosine monophosphate (cyclic AMP). Without sufficient adenylate cyclase activity to stimulate the synthesis of cyclic AMP, the flow of messages in the brain in terms of action potentials and neurotransmitters would be disrupted.

In effect, these two enzymes serve the function of keeping neurochemical messages flowing uninterruptedly in the brain. The first enzyme is involved with neurochemicals that keep messages flowing between the cells, whereas the second enzyme is involved with processes that keep messages moving through the interior of the cell. Alcohol in large quantities can disrupt the functioning of both of these enzymes. Moreover, the activity levels of both enzymes have been shown to be significantly lowered in alcoholics in response to alcohol or appropriate stimulation. With regard to the long-term effects of alcohol use, abnormal functioning of adenylate cyclase has been reported in alcoholics with even as much as four years of sobriety.[19] Because enzymatic activity in the brain is linked to feelings of well-being and other emotional states, it is tempting to speculate about such activity in either the origins of alcoholism or in its maintenance once a person has established a pattern of heavy drinking. One way to find out if these problems with an enzyme like adenylate cyclase precede active alcoholism or are a result of it would be to study the enzyme in children of alcoholic parents before they start to drink or in adult children of alcoholics who have never drunk.

A greater incidence of enzyme abnormalities in alcoholic offspring would suggest that these problems are more than merely an outcome of heavy drinking but may actually be genetic, biologic deficiencies linked to the origins of alcoholism.

Brain Condensation Products

Still another approach to the biologic or disease basis of alcoholism involves studying certain products thought to be formed in the body when people drink alcohol. Whether we drink alcohol as wine, beer, or liquor, once in the body it is promptly changed to a substance called acetaldehyde, which in turn is changed to acetic acid. Before its transformation, however, acetaldehyde can react with the various neurotransmitters in the brain to form still other products. These new chemicals formed by acetaldehyde reacting with neurotransmitters are called condensation products.

The most important condensation products are salsolinol, tetrahydropapaveroline, and β-carbolines. The first two of these products are called tetrahydroisoquinolines (THIQs), which are a family of chemicals formed by acetaldehyde reacting with dopamine or another aldehyde in the brain called dopaldehyde. β-Carbolines, on the other hand, are formed when acetaldehyde reacts with the neurotransmitter serotonin.

When either the THIQs or β-carbolines are infused into the brains of rats or monkeys, these animals begin to drink large quantities of alcohol. Myers, a leader in the research on these condensation products, has reported that after being treated with THIQs, monkeys have consumed as much as the equivalent for humans of two quarts of 80-proof liquor a day for many days.[20]

What is it about these chemicals that can cause such changes in the drinking of research animals? One of the THIQs, tetrahydropapaveroline, appears to be similar to an alkaloid precursor of morphine. In effect, the theory is that tetrahydropapaveroline produces addictive drinking because it is similar to a narcotic.

Heavy drinking after β-carboline infusions into the brain is thought to occur in another way. When β-carbolines are infused into the brains of animals, the animals respond with panic and anxiety. Apparently it is these uncomfortable states of high anxiety that lead to increased drinking.

While the research on THIQs and β-carbolines is interesting, we cannot conclude that these condensation products cause alcoholism in humans. To be sure, infusing these substances into animals' brains dramatically affects their drinking behavior, but uncertainty exists over whether all of these products are actually formed in the human body when alcohol is consumed. The evidence is mixed. Salsolinol is clearly formed in the brain, and there is strong evidence to support this.[21] On the other hand, only one recent study has found evidence for the formation of tetrahydropapaveroline in the brain.[22] Nobody has yet shown the formation in the brain of a type of β-carboline produced by a reaction between acetaldehyde and serotonin.[23] In addition, because in theory both alcoholics and nonalcoholics produce THIQs, it is unclear why alcoholism develops in some but not in others.

The THIQ and β-carboline theories of the origin of alcoholism, like virtually all scientific theories, have important missing pieces of scientific data. Nonetheless, they remain intriguing bodies of research and theory about the origins of alcoholism.

The New Disease Model: A Biopsychosocial Disease

As we have come to understand, alcoholism is not only a psychosocial and sociocultural problem but a biologic problem as well. Given genetic predispositions and a psychosocial environment that encourages repeated exposure to alcohol, illness predictably results. Appreciating the underpinnings of the disease and the sociocultural contexts in which it gets expressed is clearly necessary if we are to understand alcoholism fully and guide its victims to recovery.

Alcoholism is a multidimensional illness; it is a biopsychosocial disease involving the body, mind, and society. This new disease model of alcoholism is a reminder that if alcoholism is to be understood, it must be seen as a human problem, one that affects all of society and not this or that part in isolation from the rest. The recent research, however, in genetics, neurochemistry, and pharmacology emphasizes the importance of biologic factors in alcoholism. Rather than a problem of will power, character, or morality, alcoholism is an illness with critical biologic dimensions that must be ap-

preciated if its devastating effects on individuals and the societies in which they live are to be stopped.

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